REMARKS

This amendment is being submitted subsequent to a telephone interview with Examiner Sines, in which the undersigned and Noam Pollack (Siemens Medical Solutions Diagnostics) compared the Buechler reference cited by the Examiner with the Applicant's invention, as now claimed. The Examiner's active participation in the discussion was much appreciated.

Claims 3-8, 11-16, and 28-38 remain in the application for further prosecution. Independent Claims 1, 9, and 27 have been cancelled and replaced with new claims 33, 34, and 35 respectively. Claims 36-38 have been added. The new claims distinguish the Buechler reference by stating that the reagent-containing absorbent substrate is positioned adjacent to (i.e. not on) the array of posts so that liquid is uniformly distributed over the substrate by the posts. The substrate may be positioned either above or below the posts or alternatively after the posts. Both positions are used in the examples, as will be described below.

Double Patenting

Claims 1-4, 6 and 8 have been provisionally rejected on the ground of non-statutory double patenting over claims 1, 4 and 6 of copending application 10/608,671. Since the claims have been amended herein, filing of a terminal disclaimer may not be needed and filing will be deferred until such time as the applications have been found allowable.

Rejections Under 35 U.S.C. § 112

Claims 1, 3-9, 11-16, and 27-32 have been rejected under 35 U.S.C. §112, first paragraph, as failing to comply with the enablement requirement. More particularly, the Examiner considered the specification to lack sufficient detail to provide the claimed lower capillary force.

Claims 1, 3-9, 11-16, and 27-32 have been rejected also under 35 U.S.C. §112, second paragraph, as being indefinite. As to Claim 1, the Examiner contends that it is unclear how the posts are arranged to provide a lower capillary force. As to Claims 9, 11-16, and 27-32 the Examiner contends that it is unclear as to how the specific structure provides a lower capillary force.

Both of the above rejections have been obviated by the amendments, in which reference to a lower capillary force has been removed. However, it should be evident that liquid flow either stops or is slowed at the entrance of a reagent-containing well where the width increases and capillary forces decrease. By contrast, Buechler provides a higher capillary force with his array of posts. The liquid does not stop but enters the distal region, even though it is wider. In the present application, Fig. 3 and 4 illustrate a typical case where liquid enters a region 34 containing an array of posts disposed to distribute liquid uniformly over a reagent-containing substrate positioned below the array of posts. As the passageway widens (32), the capillary force is reduced and additional force may be applied to overcome the decrease in capillary forces. This may be centrifugal force or, as described in Example 4, externally-applied pressure can be used.

Rejections Under 35 U.S.C. § 102

Claims 1, 3, 5, 6, 9, 11, 13 and 14 have been rejected again under 35 U.S.C. § 102(b) as anticipated by Buechler (U.S. 6,113, 855). Claims 1 and 9 have been replaced by new claims 33 and 34.

Buechler's patent is principally directed to improving the flow from one region of his assay device to another larger region, despite the need for additional space to accommodate the

extra volume of added reagents. He solved his problem by adding structures to <u>increase</u> capillary forces in the larger region (see column 3, lines 3-15). However, Buechler provided only cursory information about the disposition of reagents in his device. Buechler was not concerned with the uniform distribution of liquids over reagent-containing absorbent substrates, which is the problem addressed by the Applicants (*see* page 9, line 20 to page 10, line 26). Buechler does not teach placing an absorbent substrate containing reagent in his device. Furthermore, in the claimed invention, the reagent-containing substrate is positioned adjacent to (i.e. above, below or after) the microstructure posts, a feature not found in Buechler.

In general, Buechler teaches that posts should provide greater capillary forces in his "distal" region, which was made larger to accommodate the liquid sample and any other liquids that may be used (see column 6, lines 44-47). Buechler disposed his posts to increase capillary force in the distal region, thereby drawing liquid out of the proximal region into the distal region where reactions occur. Liquid moving by capillary force through a capillary passageway will naturally stop or slowdown at the inlet of a large chamber when capillary force decreases. In Buechler, the posts were spaced to create an increased capillary force. This was not desired by the Applicants, who wanted to distribute liquid uniformly over an absorbent substrate and who reduce capillary forces for that purpose.

The Applicant's claims state that an absorbent substrate containing reagents is positioned <u>adjacent</u> the posts. More particularly, the substrate maybe below the posts (see Fig. 3), above the posts, or after the posts, as shown in the examples and discussed below. Buechler says little, but appears to place reagents <u>on</u> his array of posts. At Column 3, lines 56-64, Buechler suggests that reagents can be bound to a "solid phase", which he then says can usefully occur in "capillary

spaces", which "should be as small as possible to improve the kinetics of the reaction". This suggests that to take advantage of the increased velocity and turbulence which will be present as liquid flows around the posts, that the reagent will be located on the posts, since it is the sides of the posts that create increased capillary forces. Buechler suggests using capillary spaces of 0.5 to 200μm and shows the space between posts to be 36.1μm (Fig. 5B), 43μm (Fig. 6B), 26μm (Fig. 7B), 10μm (Fig. 8B), and 12μm (Fig. 9B). Thus, one can conclude that Buechler's reagents were located directly on the posts where the capillary forces are greatest. Consequently, he teaches away from the Applicants' device. Therefore, one skilled in the art would not expect that placing reagent-containing absorbent substrates in a region of low capillary force would be advantageous. Furthermore, Buechler says that he leaves space above the tops of his posts, which filled with liquid and was outside the array of posts with their increased capillary forces. See column 8, lines 5-7, 29-34, and 55-57 and column 9, lines 14-17, and 38-40. There is no suggestion that the space above the array of posts was used for any purpose, certainly not to contain absorbent substrates.

Buechler apparently was not concerned with the problems associated with directing liquids uniformly over absorbent substrates containing reagents. Distributing a sample liquid uniformly over a reagent-containing substrate produces most accurate results. The Applicant's have found, contrary to the Buechler invention, that increasing capillary forces in the reagent-containing chamber leads to bypassing of the reagent-containing substrate and failure to remove all of the air originally in the chamber. While an array of posts may be used, they should not provide increased capillary forces, but should slow down the liquid flow and distribute it over an adjacent substrate, while pushing out the air. Both are needed to assure uniform distribution of liquids onto absorbent substrates.

The presence of the reagent-containing substrate alone is not sufficient to assure uniform distribution of the liquid over the substrate. Bypassing of the substrate can occur, thereby trapping air and preventing uniform absorption of liquid by the absorbent substrate. When an array of posts is included, the liquid is distributed uniformly over the substrate. In the alternative case, where the array of posts is present, but with no substrate, the posts are bypassed since the capillary forces are greater at the chamber walls than through the array of posts. Thus, it is the combination of an array of posts with an adjacent reagent-containing substrate that is able to distribute liquid uniformly over the substrate, while pushing out the air. This was illustrated in the previously-submitted declaration by one of the Applicants. A copy of that declaration, including a set of colored photographs, is enclosed.

Substrates in the Examples

Porous substrates typically have small pores which provide a greater capillary force than an array of microposts. The posts distribute the liquid uniformly over the porous substrate while pushing air ahead of the liquid. At the same time the porous substrate imbibes the liquid and pushes air contained in the pores ahead and eventually out the air vent. Typically, two types of porous substrates are used in assays, those that distribute liquids uniformly in all directions at the same time, or those that distribute liquids uniformly in only one direction, that is, a linear flow type. Both types are illustrated in the application's examples.

In the examples, reagent-carrying substrates are located adjacent to microstructures which assist in distributing liquids over the substrates. Figures 3 and 4 illustrate the use of an array of posts (35) located above and in contact with the reagent-containing substrate (in 34), which in Example 4 is a glucose reagent on a Pall biodyne porous membrane

(page 18, lines 5-6). The Comparative Example (page 19) states that when the array of microposts was not present the liquid trapped air in the chamber, thus implying that the liquid passed too rapidly through region 34 and reaches the air vent 38, thereby preventing air from being expelled.

Example 1 illustrates a use of the devices shown in Fig. 1, where chamber 24 contains a fibrous pad is used in association with microstructures. From the drawing it can be seen that chamber 24 is similar to the chamber shown in Fig. 3 & 4. A uniform distribution in all directions over the fibrous pad for incubation with antibodies is needed prior to the reaction with an agglutinator in chamber 26, which illustrates the second type of porous substrate, where liquid moves uniformly in one direction (i.e. linear flow). A porous microcellulose substrate is striped with varying concentrations of the reagent. Thus, the reaction of the striped reagent indicates the concentration of HbA1c in the sample liquid. The labeled sample is distributed onto the strip by microstructures at the inlet of chamber 26. Thus, in chamber 26 the microstructures are before the absorbent substrate. Another absorbent material is used in well 32 to assist movement of the liquid along the treated substrate in agglutination chamber 26.

Example 2 is similar to Example 1, except that chamber 26 is located so that the liquid flow flows "uphill", that is toward the center of rotation of the microfluidic device when centrifugal force is used to move the liquid through the device. Clearly, the absorbent substrate is of the linear flow type, since the capillary flow is opposed to any centrifugal force that may be applied. Note also that in Example 2 (Fig. 2) that a microstructure ramp 34 is used to direct the liquid into a plateau on which the agglutination stop is placed. In Example 3, the labeled sample is introduced at the center of the agglutination strip, which wicks in two directions. This confirms that the porous strip is of the linear flow type.

Rejections Under 35 U.S.C. §103

Claims 4 and 12 have been rejected under 35 U.S.C. 103(a) as unpatentable over Buechler in view of Peters (U.S. 6,296,126). If Claims 33 and 34 are found patentable over Buechler, then Claims 4 and 12 also should be patentable. Peters does teach the use of posts with wedge-shaped cutouts, but he positions them so as to act as channels to empty capillaries. As Peters notes at column 3, lines 56 *et seq.*, his device is based on the "suction action" of the wedge shaped cut-outs. In the present invention, the wedge shaped cut-outs are optional and are positioned 90 degrees from the direction in which the liquid flows across the well.

The Examiner argues that the person of ordinary skill in the art would recognize that wedge-shaped cut outs would provide "effective fluid control". However, while Peters uses his wedge-shaped cutouts as open capillaries to empty capillary channels, in the Applicants' device the cutouts are positioned to receive liquid flowing around the array of posts and they would not act as open capillaries because they would receive liquid along the cutout, rather than at one end, as Peters teaches.

Claims 7, 8, 15, 16, 27, 28 and 30-32 have been rejected under 35 U.S.C. 103(a) as unpatentable (i.e. obvious) over Buechler in view of Columbus (U.S. 4,233,029). Claims 7 and 8 depend from new Claim 33 and should be allowable. Claims 15 and 16 depend from new Claim 34 and also should be allowable. Claim 27 has been canceled and replaced by new Claim 35. Claims 28 and 30-32 depend from new Claim 35 and also should be allowable.

As shown in Columbus '029, liquid is introduced at a central location from which it flows in all directions over the opposed set of grooves. The Applicants' device is entirely different since it enters one side of the inlet chamber and distributes liquids over the reagents in the

chamber. Despite the Examiner's contention, the Columbus device is in no sense modified for use in the Applicants' device. Columbus uses his grooves to spread liquid over 360°, while the Applicants' liquid enters the reagent-containing well and flows across the groove (or weir) in one direction as it flows generally toward the array of posts. At most, using Columbus as a secondary reference involves both hindsight and selective use of the Columbus teachings.

Claims 9, 11, 13, and 14 have been rejected under 35 U.S.C. 103(a) as unpatentable over Buechler. Claim 9 has been canceled and replaced by new Claim 34 to include the distinguishing features discussed above in connection with Claim 33. That is, the device locates the reagent-containing absorbent substrate adjacent (not on) the array of posts, so that the liquid passing around the posts can be uniformly distributed over the reagent-containing absorbent substrate. Therefore Claim 34 and its dependent claims should be allowable.

Claim 29 has been rejected under 35 U.S.C. 103(a) as unpatentable over Buechler and Columbus in view of Peters. Claim 29 has been canceled and replaced with new Claim 35. The deficiencies of Columbus and Peters have been discussed above. Columbus directs liquid flow in all directions, not in one direction as in the Applicant's device. Peters positioning of his wedge-shaped cutouts and their method of use differs from the Applicants and therefore could not be obvious. Peters used his wedge-shaped cutouts as open capillaries to transport liquid from closed capillary passageways. In the Applicants' device, the entire length of a cutout receives liquid so that they would not serve as open capillaries.

In view of the amendments and the above remarks the Examiner is urged to allow the amended claims. If further amendments are believed necessary, the Examiner is invited to contact the Applicant's attorney at the telephone number provided below.

Respectfully submitted,

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